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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
ZARA, JANE J	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 09/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/340,595	PODHAJCER ET AL.	
	Examiner	Art Unit	
	Jane Zara	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *55,56,58 and 59* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *55,56,58 and 59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office action is in response to the communication filed 4-5-04.

Claims 55, 56, 58 and 59 are pending in the instant application.

The finality of the Office action mailed 4-20-04, and the allowability of claims 55, 56, 58 and 59 are hereby withdrawn in light of the rejection and remarks set forth below.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Arguments and Amendments

Withdrawn Rejections

Any rejections not repeated in this Office action are hereby withdrawn.

New Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 55, 56, 58 and 59 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 55, at line 6, recites the "reverse complement of nucleotides 15-1698 of SEQ ID NO: 1." It is unclear what the "reverse complement" is referring to. This is a double negative, and the reverse of the complement is actually

nucleotides 15-1698 of SEQ ID NO: 1, and NOT an antisense of this region of the sequence (e.g. omitting "reverse" would be remedial).

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 55, 56, 58 and 59 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the in vivo inhibition of human osteonectin of SEQ ID NO: 1 comprising the administration of transfected IIB-MEL-LES melanoma cells previously transfected in vitro with a nucleic acid sequence that expresses the complement of nucleotides 15-1698 of SEQ ID NO: 1, whereby tumor growth of the administered and previously transfected cells is inhibited, does not reasonably provide enablement for the in vivo targeting and inhibition of expression of human osteonectin of SEQ ID NO: 1 comprising the administration of antisense, or further whereby treatment effects are provided in an animal. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with these claims.

The claims are drawn to methods of treating a melanoma tumour in a human comprising the subcutaneous administration to tumour cells of an antisense nucleic acid comprising expressing the complement of nucleotides 15-1698 of SEQ ID NO: 1.

The following factors have been considered in determining that the specification does not enable the skilled artisan to make and/or use the invention over the scope claimed.

The state of the prior art and the predictability or unpredictability of the art. The following references are cited herein to illustrate the state of the art of antisense treatment in organisms. Branch and Crooke teach that the in vivo (whole organism) application of nucleic acids (such as antisense) is a highly unpredictable endeavor due to target accessibility and delivery issues. Crooke also points out that cell culture examples are generally not predictive of *in vivo* inhibition of target genes (A. Branch, Trends in Biochem. Sci. 23: 45-50, document "BA" in IDS filed 11-17-03, *see* entire text for Branch; S. Crooke, Antisense Res. and Application, Chapter 1, pp. 1-50, especially at 34-36).

Likewise, Peracchi cautions investigators in the field of gene therapy about the problems of achieving in vivo efficacy using oligonucleotide based approaches: "Much progress has been made towards understanding the structure and mechanism of these catalysts [ribozymes]...Despite this, it is not yet clear whether these molecules can be developed into clinically useful pharmaceutical preparations." (A. Peracchi et al, Rev. Med. Virol., 14: 47-64, abstract on page 47 and p. 51). Peracchi cites stability and delivery obstacles that need to be overcome in achieving desired in vivo efficacy: "A crucial limit of ribozymes in particular, and of oligonucleotide-based drugs in general, lies in their intrinsically low ability to cross biological membranes, and therefore to enter the cells where they are supposed to operate...cellular uptake following systemic

administration appears to require more sophisticated formulations... the establishment of delivery systems that mediate efficient cellular uptake and sustained release of the ribozyme remains one of the major hurdles in the field." (*Id.* p. 51). In addition, Wu et al teach an inverse correlation between rate of nucleic acid uptake by target cells and the size of the nucleic acid molecule (USPN 6,030,954, col. 9, lines 41-60).

Tamm et al, in a review article discussing the therapeutic potential of antisense in treating various forms of neoplasia, conclude that "Proof of clinical efficacy, of any of the antisense oligonucleotides in the field of oncology, is still missing." (Tamm, I. et al. The Lancet, 358 : 489-497, especially at 490-493 for a summary of various clinical trials in process using antisense). Additionally, Agrawal et al point to various factors contributing to the unpredictability of antisense therapy, including non-antisense effects attributed to secondary structure and charge, as well as biological effects exerted by sequence motifs existing within the antisense sequences, all providing for unpredictable in vivo side effects and limited efficacy (S. Agrawal et al., Molecular Med. Today, 6: 72-81, at 72-76 and 80). Agrawal et al speak to the unpredictable nature of the antisense field thus: "It is therefore appropriate to study each antisense oligonucleotide in its own context, and relevant cell line, without generalizing the results for every oligonucleotide." (*Id.* at 80). Cellular uptake of antisense oligonucleotides by appropriate target cells is another rate limiting step that has yet to be overcome in achieving predictable clinical efficacy using antisense. Both Chirila et al and Agrawal et al point to the current limitations which exist in

our understanding of the cellular uptake of antisense oligonucleotides in vitro and in vivo (see Agrawal et al especially at pages 79-80; see Chirila et al., Biomaterials, 23: 321-342 in its entirety, especially at 326-327 for a general review of the "important and inordinately difficult challenge" of the delivery of therapeutic oligonucleotides to target cells).

The amount of direction or guidance presented in the specification AND the presence or absence of working examples. Applicants have not provided guidance in the specification toward a method of treating tumours, melanoma or otherwise, in an animal comprising the administration of antisense oligonucleotides or nucleic acids expression the complement of nucleotides 15-1698 of SEQ ID NO: 1. The specification teaches the in vitro transfection by calcium phosphate of previously cultured IIB-MEL-LES melanoma cells with a nucleic acid that expresses the antisense nucleic acid that is the complement of nucleotides 15-1698 of SEQ ID NO: 1, and the subsequent subcutaneous injection of these transfected cells into the flank of nude mice, whereby transfected tumour cell growth is inhibited. One skilled in the art would not accept on its face the examples given in the specification of the in vitro transfection and subsequent injection of transfected cells into mice as being correlative or representative of the successful in vivo delivery, targeting and inhibition of human osteonectin of SEQ ID NO: 1 in an animal and further whereby treatment effects are provided in that animal for melanoma tumours in view of the lack of guidance in the specification and the known unpredictability associated with the targeting, efficient cellular uptake and inhibition of a target gene in an organism using

antisense (or nucleic acids expression antisense) and further whereby treatment effects are provided for melanoma in that organism.

The breadth of the claims and the quantity of experimentation required. The claims are broadly drawn to methods of treating a melanoma tumour in a human comprising the subcutaneous administration to tumour cells of a nucleic acid molecule expressing the antisense nucleic acid comprising the complement of nucleotides 15-1698 of SEQ ID NO: 1. The quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of accessible target sites, modes of delivery and formulations to target appropriate (melanoma) cells and /or tissues harboring the target osteonectin of SEQ ID NO: 1 whereby the antisense is expressed in sufficient quantity, target gene expression is inhibited by the expressed antisense construct in target cells in vivo and treatment effects are provided for any melanoma tumour in an animal. Since the specification fails to provide any particular guidance for targeting appropriate cells harboring the osteonectin of SEQ ID NO: 1 using the nucleic expression construct encoding the antisense of 1.6 kilobases that complements nucleotides 15-1698 of SEQ ID NO: 1 in an organism, and since determination of these factors is highly unpredictable, it would require undue experimentation to practice the invention over the scope claimed.

Applicant's arguments filed 6-26-01, 12-3-01, 1-3-03, 8-26-03 and 2-13-04 have been fully considered but they are not persuasive. Applicants argued that the examiner, in expressing concerns regarding the ability to deliver sufficient

quantities of the nucleic acid construct encoding the antisense molecule comprising 1.6 kilobases that complements nucleotides 15-1698 of SEQ ID NO: 1 to the appropriate target cell(s) in an organism, whereby target gene inhibition is obtained and treatment effects are provided, are misplaced because i.) the reliance on 1995 publications is misplaced; ii.) methods for in vivo delivery were well known in the art before the instant invention (which claims a priority date of 2-12-97); iii.) the instant invention involves direct injection into a tumor site and not systemic administration of distal target cell delivery issues; iv) down regulation of osteonectin expression completely prevented tumor formation in mice and induced a dominant "bystander" effect, thereby providing that not all tumour cells need be transfected with antisense polynucleotide. These arguments are addressed below.

Contrary to Applicants' assertions, the scope of enablement rejection presented in this Office action relies on references that post-date the filing and claimed priority dates of the instant invention. The teachings of Branch (1998), Crooke (1998), Agrawal (2000), Chirila (2002), Tamm 2001) and Peracchi (2004) each stress that delivery issues are unpredictable for gene therapy approaches, that in vitro results cannot be extrapolated to in vivo conditions, and that sufficient delivery and/or expression of the antisense nucleic acid molecule, and subsequent inhibition of target gene expression in the appropriate target cell(s) must be empirically determined for a particular antisense, target cell and target gene (see pp. 4-6 of this Office action). Applicants also argue that since the instant invention involves direct injection of the inhibitory nucleic acid construct

into tumour cells, delivery issues are less of a concern than if, e.g. distal target cell delivery was intended. Applicants are correct that direct injection of a nucleic acid construct is perhaps less of an obstacle than distal target cell delivery following systemic administration, nevertheless, the sufficient delivery, uptake and expression of the inhibitory nucleic acid molecule is required for the instant invention to be enabled for in vivo target gene silencing and treatment effects. The successful in vitro transfection of target cells and subsequent implantation of these transfected tumour cells are not representative of the ability to directly inject a tumour and provide treatment effects in an organism. In vitro transfection (e.g. using calcium phosphate) is a routine technique used to introduce sufficient quantities of nucleic acid molecules into isolated, dissociated and extensively manipulated target cells in a flask. In vitro transfection using this standard technique is not representative of sufficient delivery of the expression vector into target cells in vivo, where the target tumour cells are not dissociated, isolated or washed. Sufficient delivery and subsequent expression of the nucleic acid construct in the target cells, whereby target gene inhibition is obtained and treatment effects provided, is established empirically and cannot be predicted or extrapolated from in vitro transfection experiments. Similarly, with the bystander effect observed for the implanted tumours generated from in vitro transfected cells - no threshold can be predicted regarding ample inhibitory nucleic acid molecule delivery, expression and obtaining bystander effects following in vivo administration. It is unclear whether the bystander effects (observed in the previously transfected and subsequently implanted cells that formed tumours)

had resulted from the subsequent expression of downstream effector molecules of these efficiently transfected cells - and were either secreted or released following transfected cell destruction in vivo (for instance, where necrotic, preveiously transfected cells caused complement activation at the tumor site, leading to bystander target cell destruction). It is also unclear whether cells contacted in vivo with the inhibitory nucleic acid construct would have sufficient inhibitory nucleic acid uptake and expression to exhibit this bystander effect. Because of the unpredictability in comparing in vitro transfected cells with in vivo target cell delivery and expression, the instant invention lacks enablement over the scope claimed.

Applicants also argue that the examiner had not met the burden of establishing a reasonable basis to question the enablement provided for the claimed invention, and that a specification disclosure which contains a teaching of the manner and process of making and using an invention must be taken as being in compliance with enablement requirement, unless there is reason to doubt the truth of the statements contained therein. There is no doubt regarding the truth of the statements contained in the instant disclosure, but, as described in the preceding paragraphs, the teachings provided in the instant disclosure are not representative of the scope claimed (e.g. in vitro transfection of cultured cells is not representative of direct injection in an animal). Furthermore, the unpredictability of gene therapy, as it currently exists, has been described on pp. 4-6 of this Office action, as well illustrated by the teachings of Crooke, Branch, Agrawal, Chirila, Tamm and Peracchi. It is thus noted that the unpredictability of

a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17, USPQ2d 1714 (BPAI 1991). Therefore, the enablement rejection is hereby reinstated.

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone number for the Group is **703-872-9306**. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(571) 272-0765.** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (571) 272-0760. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (571) 272-0564. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

JZ
9-8-04

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